

REMARKS

The Examiner has rejected claims 1 and 3-10 for obviousness-type double patenting over claims 1-24 of U.S. Patent No. 6,387,621 (the '621 patent) in view of Herrmann et al. Thus, the Examiner is suggesting that the subject matter of claims 1 and 3-10 is an obvious variant of the invention claimed in the '621 patent in view of the disclosure of Herrmann et al. The Applicant respectfully traverses the Examiner's rejection of claims 1 and 3-10 for obviousness-type double patenting. Claims 1 and 3-10 are not obvious over the '621 patent claims in view of Herrmann et al.

The claims of the present application specify at least the steps of generating a plot wherein the fluorescence values are recorded for each amplification cycle, performing a confidence band analysis on the plot to generate a positive or negative call, and if the call is positive, confirming the positive call by a melting temperature analysis.

Generally, the '621 patent claims are directed to performing a polymerase chain reaction (PCR) in which a baseline fluorescence region is established by confidence band analysis, and ascertaining whether the fluorescence value during a selected amplification cycle is outside the baseline fluorescence region. As conceded by the Examiner, the '621 patent claims do not specify "confirming the results by using a melting temperature analysis." The Examiner cites Herrmann et al. to provide the teaching of using a melting temperature analysis because the '621 patent claims lack this teaching.

There is no motivation to combine the '621 patent claims with Herrmann et al. As conceded by the Examiner, the '621 patent claims do not specify "confirming the results by using a melting temperature analysis." See page 4, lines 1-2 of the Office Action. With respect to Herrmann et al., the Examiner indicates that Herrmann et al. teaches "performing a PCR reaction followed by confirming the target using a melting temperature analysis." See page 4, lines 3-4 of the Office Action. Thus, neither the '621 patent claims nor Herrmann et al. expressly suggests

combining the two steps of 1.) confirming a positive call generated by confidence band analysis by and 2.) using melting temperature analysis as a second confirmation step.

The Examiner cites *Ruiz v. A.B. Chance Company* (Fed. Cir. 2004) in which the court stated that an “an examiner may find a motivation to combine prior art references in the nature of the problem to be solved.” The Examiner further states that the “nature of the recognized problem in U.S. Patent No. 6,387,621 lends itself to solution by combination with the Hermann reference.” See page 12, lines 3-4 of the Office Action.

The Examiner also refers to express statements in the ‘621 patent and in Herrmann et al. that the Examiner argues provide motivation to combine because, according to the Examiner, these statements indicate that Herrmann et al. solves the problem recognized in the ‘621 patent. To support his motivation to combine arguments, the Examiner points to the statements in Herrmann et al. that “[t]he ability to multiplex PCR analysis by color and T_m has many uses in addition to multiplex genotyping. For example, internal amplification controls are often needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR quantification (see page 428, column 1).” See page 4, line 22 through page 5, line 5 of the Office Action.

To support his motivation to combine arguments, the Examiner also points to statements in the ‘621 patent. For example, the Examiner states on page 11, lines 3-11 of the Office Action that “[a]s noted previously it would have been *prima facie* obvious to combine Hermann with any analytical PCR method to improve the specificity and validity of the method for the reasons cited from the Hermann paper. This additional verification solves the problem, recognized by U.S. Patent No. 6,387,621, that “accurately discriminating between positive and negative samples is not easy in practice (see column 6, lines 15-16).” The specification continues, noting “Automatic identification of the background is surprisingly difficult. (see column 6, lines 48-49).” Hermann provides one solution for this problem by providing a means

to accurately discriminate between positive and negative PCR samples such as those used by U.S. Patent No. 6,387,621.”

The Examiner indicates that these statements provide motivation to a skilled artisan to combine Herrmann et al. with the '621 patent claims because the '621 patent indicates that accurately discriminating between positive and negative samples is difficult, and Herrmann et al. provides a solution to this problem by “providing a means to accurately discriminate between positive and negative PCR samples.” See page 5, lines 15-16 of the Office Action.

Contrary to the Examiner’s argument, accurate discrimination between positive and negative samples in the context of the '621 patent means determining the presence of a nucleic acid in a sample without analysis or comparison to different signals resulting from different nucleic acids in the sample (*i.e.*, by confidence band analysis). In contrast, melting temperature analysis in the context of Herrmann et al. is used to determine the presence of a nucleic acid in a sample by analyzing and comparing different signals resulting from different nucleic acids in the sample. Herrmann et al. is limited to the use of melting curve analysis in the context of discriminating between multiple DNA’s (*i.e.*, multiple signals) in a PCR sample. Herrmann et al. solves a completely different problem than is recognized in the '621 patent or than is specified in the claims of the '621 patent. Accordingly, there is no motivation to combine the '621 patent claims with Herrmann et al. based on the nature of the problem to be solved because completely different problems are solved by the '621 patent and Herrmann et al.

As discussed above the Examiner has cited statements from Herrmann et al. on page 4, line 22 through page 5, line 5 of the Office Action that the Examiner argues provide express motivation to combine by providing a solution to the problem identified in the '621 patent. Each of the statements from Herrmann et al. cited by the Examiner is directed to using melting temperature analysis to discriminate between multiple DNA’s in a PCR sample by analyzing and comparing different signals resulting from each of the different nucleic acids in the sample. The statements cited by the Examiner are directed to discrimination between multiple

DNA's 1.) in the context of multiplex genotyping, 2.) in the context of discrimination between an internal amplification control and the target DNA, and 3.) in the context of discrimination between a competitor as an internal standard and the target DNA. These statements in Herrmann et al. are unambiguously limited to the use of melting curve analysis in the context of multiplex experiments. In other words, Herrmann et al. is unambiguously limited to the use of melting temperature analysis to **discriminate between multiple DNA's in a PCR sample**. The discrimination is achieved by analyzing and comparing the different signals that result from each of the different nucleic acids in the sample.

As discussed above discriminating between multiple DNA's in a PCR sample by analyzing and comparing the different signals that result from each of the different nucleic acids in the sample is not the problem identified in the '621 patent. The statements from the '621 patent cited by the Examiner on page 11, lines 3-11 of the Office Action that "accurately discriminating between positive and negative samples is not easy in practice (see column 6, lines 15-16)" and "[a]utomatic identification of the background is surprisingly difficult. (see column 6, lines 48-49)" refer to accurate discrimination between positive and negative samples in the context of determining the presence of a single nucleic acid in a sample without analysis or comparison to different signals resulting from other nucleic acids in the sample.

Hermann et al. does not provide a solution to this problem. To the contrary, melting temperature analysis in the context of Herrmann et al. is used to determine the presence of a nucleic acid in a sample by analyzing and comparing different signals resulting from different nucleic acids in the sample. Thus, Herrmann et al. does not provide a solution to the problem identified in the '621 patent so the combination of the express statements identified by the Examiner in the '621 patent and Herrmann et al. cannot provide motivation to combine the references, and cannot render obvious the Applicant's claimed method over the combination of the '621 patent claims and Herrmann et al. Accordingly, there is no motivation to combine the references either in the express statements in the '621 patent and Herrmann et al. or in the nature of the problem to be solved, and the Applicant's claimed method is not obvious over the '621

patent claims in view of Herrmann et al. Withdrawal of the rejection of claims 1 and 3-10 for obviousness-type double patenting is respectfully requested.

The Examiner also rejected claims 1 and 3-10 under 35 U.S.C. § 103(a) over Wittwer in view of Herrmann et al. Wittwer is the European counterpart of the '621 patent. The Examiner made the same substantive arguments for rejecting claims 1 and 3-10 under 35 U.S.C. § 103(a) based on Wittwer in view of Herrmann et al. as the Examiner made for rejecting claims 1 and 3-10 for obviousness-type double patenting. Accordingly, the Applicant's arguments made with respect to the obviousness-type double patenting rejection apply with equal force to this rejection except that the text of Wittwer is applicable rather than the claims of the '621 patent. Withdrawal of the rejection of claims 1 and 3-10 under 35 U.S.C. § 103(a) over Wittwer in view of Herrmann et al. is respectfully requested.

CONCLUSION

The foregoing remarks are believed to fully respond to the Examiner's rejections. The claims are in condition for allowance. Applicant respectfully requests allowance of the claims, and passage of the application to issuance.

Respectfully submitted,
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